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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/189,130	11/10/98	HOUCK J	47.653.1

021874
DIKE BRONSTEIN ROBERTS & CUSHMAN
130 WATER STREET
BOSTON MA 02109-4280

HM11/0624

EXAMINER	
BORIN,M	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 06/24/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

Office Action Summary	Application No. 09/189,130	Applicant(s) Houck et al.
	Examiner M. Borin	Group Art Unit 1654

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-23 is/are pending in the application.

Of the above, claim(s) 9-23 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-8 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Status of Claims

1. Claims 1-23 are pending.

2. Applicant's election without traverse of Group I, claims 1-8, in communication filed 04/29/99 (paper No.6) is acknowledged. Claims 9-23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected groups.

Information Disclosure Statement

3. Applicants' Information Disclosure Statement filed 03/04/99 has been received and entered into the application. Accordingly, as reflected by the attached completed copies of forms PTO-1449, the cited references have been considered.

Drawings

4. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Sequence Listing

5. This application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), such as tetrapeptides recited in claim 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825.

Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c). A copy of the "Sequence Listing" in computer readable form has not been received as required by 37 C.F.R. 1.821(e). Applicant must provide: 1. An initial computer readable form (CRF) copy of the "Sequence Listing"; 2. An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification. 3.A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Claim Rejections - 35 U.S.C. § 103.

6. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the

obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kermode and Ferry.

The instant claims are drawn to pharmaceutical composition comprising a formyl Met peptide having formula f-Met-Leu-X, wherein X is selected from the group consisting of Tyr, Tyr-Phe, Phe-Phe, and Phe-Tyr. In particular, the formyl Met peptide analog is f-Met-Leu-Phe-Phe (claim 2) or f-Met-Leu-Tyr (claim 3).

Kermode et al. teach that neutrophils play a major role in body's defense mechanism against infectious microorganisms and that biological responses of these cells can be triggered by chemotactic formyl Met peptides. The reference discloses that formyl Met peptides, such as f-Met-Leu-Phe, f-Met-Leu-Phe-Phe and f-Nle-Leu-Phe-Tyr, bind to specific receptors on neutrophil membranes and elicit neutrophil degranulation. In particular, f-Met-Leu-Phe-Phe (i.e., peptide of the instant claim 2) is one of the most potent formyl Met peptides analogs. Degranulation response is well correlated with the receptor binding. See p.276, first paragraph; Tables 1,2; Fig.2;p. 719. Kermode teaches that the rabbit peritoneal neutrophils used in the study are an adequate *in vitro* model as they have proved suitable for detailed biological characterization of the biological responses of neutrophils to chemotactic peptides. See p. 1991, left column, last paragraph.

Similarly to Kermode reference, Ferry et al. teaches that multiple effects of formyl Met peptides include adhesion, chemotaxis, superoxide production and lysosomal enzyme release in neutrophil leukocytes. See p. 61, first paragraph. In particular, the reference teaches formyl Met peptide, f-Met-Leu-Tyr (i.e., peptide of the instant claim 3).

The above references differ from the presently claimed invention by failing to explicitly disclose the use of formyl-Met peptides as pharmaceuticals.

It would have been *prima facie* obvious to one of ordinary skill in art at the time the invention was made to be motivated to make and use pharmaceutical composition comprising formyl-Met peptides, in particular f-Met-Leu-Phe-Phe and f-Met-Leu-Tyr taught by Kermode and Ferry, because both references teach that formyl-Met peptides possess useful biological properties as they stimulate various functions of neutrophils which constitute defense reaction to infectious microorganisms. One would expect that *in vitro* observations of the effect of formyl-Met peptides on neutrophils will be translated into similar *in vivo* effect, because Kermode teaches that the rabbit peritoneal neutrophils is an adequate *in vitro* model as they have proved suitable for detailed biological characterization of the biological responses of neutrophils to chemotactic peptides.

Further, it is well known that pharmaceuticals are usually dispensed in either liquid or solid carriers. One of primary skills in the art would have known that compound "X" would have had to be formulated in some manner so as to make it useful pharmaceutically

8. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kermode and Ferry, supra in view of Anderson. Two peptides encompassed by the instant claim, which have not been considered in the preceding rejection and which are not explicitly taught in the primary references, are f-Met-Leu-Phe-Tyr and f-Met-Leu-Tyr-Phe.

Anderson teaches that the requirements for the core structure of biologically active formyl Met peptide analogs are the following: N-acyl formyl group, a Met or Nle residue in position 1, Leu, Val or Ile residue in position 2, and an aromatic amino acid in position 3; a formyl Met peptide analog can be either a tripeptide or a tetrapeptide. See p. 253, Discussion section, first paragraph. As an example, Anderson teaches such formyl Met peptides as f-Met-Leu-Phe, f-Met-Leu-Tyr. See Table 2.

In regard to the instantly claimed peptide f-Met-Leu-Phe-Tyr, it would have been *prima facie* obvious to one of ordinary skills in art at the time the invention was made to be motivated to substitute Nle for Met residue in position 1 of the peptide f-Nle-Leu-Phe-Tyr reported by Kermode, because Anderson teaches that biological activity of the peptides is retained when the residue in position 1 is either Nle or Met. One would expect that formyl Met peptide analog obtained by such substitution would have the same biological properties, i.e., activate functions of neutrophils.

In regard to the instantly claimed peptide f-Met-Leu-Tyr-Phe, it would have been *prima facie* obvious to one of ordinary skills in art at the time the invention was made to be motivated to substitute Phe for Tyr residue in position 3 of the peptide f-Nle-Leu-Phe-Phe reported by Kermode, because Anderson teaches that the residue in position 3 can be an aromatic amino acid, such as Phe

or Tyr (see examples in Anderson, Table 2, lines 1, 2). One would expect that formyl Met peptide analog obtained by such substitution would have the same biological properties, i.e., activate functions of neutrophils.

9. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kermode, Ferry, and Anderson as applied to claims 1-3 above, and further in view of Gleisner. The above rejections over Kermode, Ferry, and Anderson emphasized that it would be obvious to use chemotactic formyl Met peptides as pharmaceuticals to trigger body's defense mechanisms because they stimulate neutrophil degranulation and other responses. Gleisner, on the other hand, teaches that formyl Met peptides can be also useful to counter an existing inflammation because, in the presence of other inflammatory agents which themselves cause neutrophil granule release, the formyl Met peptides inhibit neutrophil granule release and histamine release caused by other "degranulators". Accordingly, the Gleisner reference provides motivation to one of ordinary skills in the art to formulate pharmaceutical compositions of formyl Met peptides taught by Kermode, Ferry and Anderson references for use in inhibiting cytokine/histamine release in the course of treatment of inflammatory disorders.

10. Claims 1, 4-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kermode, Ferry, Anderson , and Gleisner as applied to claims 1-3 in the rejections above, and further in view of Goodman and Gilman.

Claims 4-8 are drawn to routes of administration (oral, inhalation, aerosol, topical, or tablet). Selection of a route of administration and appropriate carriers is an art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art. See, e.g., Goodman and Gilman, p. 4-9.

Prosecution by Executor

11. It is noticed that the sole inventor of the application as originally filed, J.C.Houck, is deceased, and an added page to the Declaration and Power of Attorney signed by Mary MacDonnald has been filed on 1/25/99 (paper No.3). Applicant must submit a request under 37 CFR 1.42 and a proof of the power or authority of the legal representative, as explained below.

The death of the inventor terminates the power of attorney and a new power from the executors is necessary if the attorney is to remain of record. See MPEP 409.01.

To execute the oath or declaration or file an application on behalf of the inventor a request under 37CFR 1.42 must be filed. No such request has been submitted.

According to 37 CFR 1.44, proof of the power or authority of the legal representative must be recorded in the Patent and Trademark Office or filed in the application before the grant of a patent. Whenever because of the death of an inventor the right of applying for and obtaining a patent for an invention devolves upon an executor or administrator, or whenever an executor or administrator desires to intervene prior to the granting of a patent, proof of the authority of such executor or administrator should in all cases be made of record in the Patent and Trademark Office by filing in

the application or recording in the assignment records a certificate of the clerk of a competent court or the register of wills that his or her appointment is still in full force and effect. Such certificate shall be signed by an officer and authenticated by the seal of the court by which the same was issued. Should such certificate of appointment be found to be insufficient for any reason, there may be required to be filed or recorded a certified and properly authenticated copy of the letters testamentary or of the letters of administration so that the scope of authority of the persons who seek to intervene may be a matter of record in this Office.

Prior art made of record

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Prossnitz et al., Kanaho et al., Freer et al., Linnekin et al., Gnessi et al. are cited to further show the state of the art. Gnessi et al. is cited to demonstrate that formyl Met peptides are also chemoattractants for spermatozoa.

Conclusion.

13. No claims are allowed

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael

Woodward can be reached on (703) 308-0254. The fax telephone number for this group is (703) 305-3014.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June 24, 1999

mlb

MICHAEL BORIN, PH.D
PATENT EXAMINER